RESEARCH PAPER

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Herpes zoster and postherpetic neuralgia in Catalonia (Spain)

Epidemiology and costs in persons aged 50 years and older

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Abbreviations: HZ, herpes zoster; PHN, postherpetic neuralgia; VZV, varicella zoster virus; y, year

The objective of the study was to analyze the descriptive epidemiology and costs of herpes zoster (HZ) and postherpetic neuralgia (PHN) in people aged ≥50 years in Catalonia (Spain). The incidence of HZ in Catalonia was estimated by extrapolating the incidence data from Navarre (Spain) to the population of Catalonia. The incidence of PHN was estimated according to the proportion of cases of HZ in the case series of the Hospital del Sagrado Corazón de Barcelona that evolved to PHN. Drug costs were obtained directly from the prescriptions included in the medical record (according to official prices published by the General Council of the College of Pharmacists). The cost of care was obtained by applying the tariffs of the Catalan Health Institute to the number of outpatient visits and the number and duration of hospital admissions. The estimated annual incidence of HZ was 31 763, of which 21 532 (67.79%) were in patients aged ≥50 years. The respective figures for PHN were 3194 and 3085 (96.59) per annum, respectively. The mean cost per patient was markedly higher in cases of PHN (916.66 euros per patient) than in cases of HZ alone (301.52 euros per patient). The cost increased with age in both groups of patients. The estimated total annual cost of HZ and its complications in Catalonia was € 9.31 million, of which 6.54 corresponded to HZ and 2.77 to PHN. This is the first Spanish study of the disease burden of HZ in which epidemiological data and costs were collected directly from medical records. The estimated incidence of HZ is probably similar to the real incidence. In contrast, the incidence of PHN may be an underestimate, as around 25% of patients in Catalonia attend private clinics financed by insurance companies. It is also probable that the costs may be an underestimate as the costs derived from the prodromal phase were not included. In Catalonia, HZ and PHN cause an important disease burden (21 532 cases of HZ and 3085 de PHN with an annual cost of € 9.31 million) in people aged ≥50 years, in whom vaccination is indicated.

Introduction

In Catalonia and Spain, as in other developed countries, varicella zoster virus (VZV) infection affects very young children: 82% of children aged 5–9 y have been infected, 92% of those aged 10–14 y and 94% of people aged at 15–34 y.[1,2] Nearly all people aged ≥50 y are infected by the virus. This means that 100% of the adult and elderly population of Catalonia harbor the VZV in their sensorial, dorsal and cranial ganglia, a situation that persists as long as cellular immunity against the virus is maintained. If immunity wanes, either due to a medical condition that affects immunity or as a consequence of age-related immune senescence, the virus may affect the skin retrogradely and cause herpes zoster (HZ).[3-6] Latent infection occurs in the majority of cases of primary VZV infection, but only 25–30% of those infected will develop HZ at some point during their life.[3-6] The 50% of individuals who reach the age of 85 y without having suffered HZ will suffer it during the remaining years of their life.[5]

The incidence of HZ clearly increases with age.[5,7] Furthermore, complications in adults and, above all, in the elderly, are very common, especially postherpetic neuralgia (PHN) (17–20%), ocular complications (4%) and neurological complications (3%).[7] To this must be added the pain that is present in all stages of HZ, whose intensity and duration may affect the quality of life of patients, especially those with PHN.[8-12]The cost of treatment, especially of PHN is also very significant.[13] For these reasons, HZ and its complications are a serious public health problem, causing a significant health and economic burden, and a significant loss of quality of life due to the pain caused by the disease and its complications.[12,13]

There is considerable information in Spain on the incidence of HZ that comes from population-based epidemiologic studies

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in the primary healthcare setting.[14-19] However, information on the epidemiology of PHN (proportion of cases of HZ that evolve to PHN, the incidence of PHN in the general population, the clinical and epidemiological characteristics of PHN, etc.) and, especially, the characteristics of pain in the different stages of HZ, is limited.

Since 2006, a vaccine against HZ (Zostavax®), with a high antigenic content, has been available, and will shortly become available in Spain.[20,21] The vaccine is indicated for immunocompetent persons aged ≥50 y.[21] The results of cost-effectiveness analyses will be basic in establishing vaccination priorities in this age group in Catalonia.[22]

The objective of the study was to analyze the descriptive epidemiology and costs of HZ and PHN in people aged ≥50 y in Catalonia (Spain). The results of this study will be useful in carrying out future cost-effectiveness studies of HZ vaccination in Catalonia.

Results

The estimated incidence of HZ in Catalonia during the period 2007–2013, obtained by extrapolating the incidence rate of Navarra (Spain) to the total population of Catalonia, was 31 763 cases per year (**Table 1**).

In the series of patients attended by the outpatient clinic of the Hospital del Sagrado Corazón de Barcelona during the period 2007–2013, 36 of the 333 cases of HZ diagnosed evolved to PHN (**Table 2**). All cases of PHN except one occurred in persons aged ≥ 50 y.

A total of 54.7% of cases of HZ were female, 67.5% occurred in people aged ≥50 y, and 4% occurred in immunocompromised patients. Only five cases (1.5%) required hospitalization due to HZ or its complications. These patients were immunosuppressed and/or with disseminated HZ and were treated with intravenous antiviral drugs for one week followed by oral treatment. Seven patients with PHN who had continuing, very-intense pain were referred to the pain clinic. No deaths were attributable to HZ or its complications.

Table 3, which shows the estimated incidence of cases of HZ and PHN according to age in Catalonia, demonstrates that the percentage of cases of HZ that evolved to PHN in people aged ≥50 y increased with age (12.28% in those aged 50–59 y and 17.54% in those aged ≥70 y). Total annual cases of PHN in people aged ≥50 y were 3085, representing 14.33% of the 21 532 annual estimated cases of HZ in this population group in Catalonia.

Table 4 shows the incidence rate of PHN per 1000 inhabitants according to age, estimated according to the absolute numbers of estimated cases of PHN and the population of Catalonia. The rates increased according to age. They were negligible in the <50 y age group and progressively increased in persons aged ≥50 y, from 0.76 per 1000 in the 50 to 59 y age group to 1.61 per 1000 in the >70 y age group. The rate was 1.14 per 1000 in the whole population aged ≥50 y.

The disease burden was concentrated in people aged ≥50 y, precisely the age group in which the vaccine is indicated (**Tables 3 and 4**).

Table 1. Annual estimated incidence* of herpes zoster by age. Catalonia, 2007–2013

Age (in years)	2013 Population	Annual estimated incidence rate (per 1000 inhabitants)	Annual estimated number of cases
0–4	398 166	1.14	454
5–9	418 716	2.55	1068
10–14	369 187	2.73	1008
15–19	336 660	1.84	619
20–24	359 968	1.98	713
25–29	425 944	1.61	686
30–34	557 342	1.84	1025
35–39	673 742	1.89	1273
40–44	627 774	2.28	1431
45–49	576 314	3.39	1954
50–54	509 661	5.86	2987
55–59	451 317	6.64	2997
60–64	399 433	8.41	3359
65–69	373 535	9.05	3380
70–74	279 563	9.60	2684
≥ 75	681 374	8.99	6125
Total	7 438 696	4.27	31 763

*Estimated by extrapolation of the incidence rates observed in Navarre[22]

Table 5 shows the preventive potential of the HZ vaccine in reducing cases of HZ in this age group according to age and the vaccination coverage achieved and based on the data on vaccine efficacy obtained by Schmader et al.[23] and Oxman et al.[20] **Table 6** shows the same analysis for PHN. In the best of cases (100% vaccination coverage), the HZ vaccine could prevent 11 849 cases of HZ and 2052 cases of PHN a year. At worst (estimated vaccine coverage of only 20%) only 2370 cases of HZ and 410 of PHN would be prevented.

The total cost of diagnosis and treatment of the first 215 patients in the series of cases attended by the outpatient department of the Hospital del Sagrado Corazón was 78 360.73 euros, of which 28 704.53 euros corresponded to drug costs and 49 656.23 euros to the cost of care (**Table 7**).

The mean cost per patient was 301.52 euros in cases of HZ that did not evolve to PHN and 916.66 euros in patients who did evolve to PHN. In both cases, the mean cost per patient increased with age and was highest in the ≥65 y age group (**Table 8**).

The percentage of the cost attributable to clinical services was greater than the

pharmacological cost, both in patients with uncomplicated HZ (65% of the total cost) and those with PHN (52% of the total cost). In fact, in these last patients, the costs of clinical services were nearly half the total costs (**Table 9**).

The total estimated annual cost of HZ and its complications in Catalonia is € 9.31 million, of which € 6.54 million is due to HZ and € 2.77 million to PHN (**Table 10**).

Discussion

The extrapolation of data on the incidence of HZ in Navarre to the population of Catalonia and the application to these data of the proportion of HZ cases that evolved to PHN observed in the series of cases diagnosed by the outpatient dermatology service of the Hospital del Sagrado Corazón de Barcelona, show an estimated annual incidence of HZ of 31 763 cases of HZ, of which 21 532 (67.79%) affect patients aged ≥50 y. The respective figures for PHN are 3194 and 3085 cases (96.59%) per annum, respectively.

The estimated incidence of HZ is probably very similar to the real incidence. A recent study has shown no significant differences in the incidence of HZ between European countries.[24] In addition, studies in Spain (Navarre,[19] Valencia,[14-16] and Madrid[18]) based on administrative data from primary healthcare show very similar results (overall incidence in all age groups of about 4 per 1000 inhabitants, although the Valencian study[14,15] did not include subjects aged <14 y). The study by Yawn et al.,[7] one of the most comprehensive epidemiological studies of HZ, found similar incidence rates to those observed in Spain, as did other studies performed in Europe,[25-29] Israel,[30] and the United States.[31]

The present study is the first in Spain to estimate the incidence of PHN by direct analysis of data from the medical records of patients and not through secondary sources (primary healthcare or hospital registers).

Our results probably somewhat underestimate the incidence of PHN. In fact, many patients in Barcelona attend private clinics in order to be attended by private dermatologists or ophthalmologists. It is also likely that some patients with severe disease who are treated by hospital specialists (oncologists, neurologists, etc.) go directly to these specialists when the first signs of HZ appear, attributing the disease to the side effects of the treatment received for the underlying disease or its complications. In the placebo group in the study by Oxman et al.,[20] the incidence of PHN was 2.13 per 1000 inhabitants per year in persons aged ≥70 y, slightly higher than the figure estimated in our study (1.61 per 1000). This supports the idea that the estimate of the incidence of PHN in Catalonia may be an underestimate. For the same reason, the percentage of cases occurring in immunosuppressed patients is also probably an underestimate.

Our results show that the disease burden of HZ is significant in Catalonia and the preventive potential of the vaccine in persons aged ≥50 y is high, both in the prevention of HZ and of PHN. In any case, since the HZ vaccine does not provide herd immunity, the impact of the intervention in the population will depend largely on the vaccination coverage achieved. If the coverage were similar to that of the influenza vaccine (60%), about 7000 cases of HZ and 1200 of PHN would be avoided annually.

The cost study presented here is the first to be made in Spain directly by quantifying the cost of diagnosis and treatment of each of the first 215 patients in the case series, which allowed us to estimate the total cost and the mean cost per patient.

The mean cost per patient was markedly higher in cases of PHN (916.66 euros per patient) than in cases presenting only with HZ (301.52 euros). The cost increased with age in both groups of patients. In patients without PHN, 65% of the costs were attributable to clinical services and 35% to drug costs. In patients with PHN, the cost of clinical services was also higher than drug costs, but to a lesser extent.

The total estimated cost probably underestimates the real costs, as the costs of the diagnosis and treatment of prodromal pain were not taken into account. Preliminary data from our case series indicate that over 60% of cases attended in 2012 have visited the family physician or the emergency room for pain relief before the appearance of the rash.

Table 2. Cases of herpes zoster (HZ) and cases evolving to postherpetic neuralgia (PHN) by age

Age group (in years)	Cases of HZ	Cases of HZ that evolved to PHN	
		Cases	Proportion
0–9	13	-	-
10–19	29	-	-
20–29	6	-	-
30–39	16	-	-
40–49	31	1	3.23%
50–59	57	7	12.28%
60–69	67	8	11.94%
≥ 70	114	20	17.54%
≥ 50	238	35	14.71%
All ages	333	36	10.81%

Source: Case series of patients diagnosed in 10 basic health areas for which the Hospital del Sagrado Corazón de Barcelona serves as the reference center.

Table 3. Estimated incidence of herpes zoster (HZ) and postherpetic neuralgia (PHN) in patients aged ≥ 50 y by age. Catalonia, 2007–2013

Age Group	Estimated cases of HZ	Estimated cases of PHN	
		Number of cases	% of cases of HZ
40–49	3385	109	3.22%
50–59	5984	735	12.28%
60–69	6739	805	11.94%
≥70	8809	1545	17.54%
≥50	21 532	3.085	14.33%
Total	24 917	3194	12.82%

Source: Case series of patients diagnosed in 10 basic health areas for which the Hospital del Sagrado Corazón de Barcelona serves as the reference center.

Table 4. Estimated incidence of postherpetic neuralgia (PHN) in Catalonia by age

Age group (in years)	Population	Estimated cases of PHN	
		Number of cases	Rate of PHN per 1000 inhabitants
0–9	816 882	-	
10–19	785 847	-	
20–29	785 912	-	
30–39	1 231 084	-	
40–49	1 204 088	109	0.09
50–59	960 978	735	0.76
60–69	772 968	805	1.04
≥70	960 937	1545	1.61
≥50	2 694 883	30 685	1.14

It may be concluded that HZ and its main complication, PHN, are an important public health problem in Catalonia. The disease burden in people aged ≥50 y (21,532 cases of HZ and 3085 cases of PHN annually, with a total annual cost of 9.31 million euros), in whom both HZ and PHN are potentially vaccine-preventable, is high.

Like all epidemiological studies, our study has strengths and weaknesses.

The main strength is that all patients were diagnosed by the same specialist dermatologist (M Salleras), who has extensive clinical experience, and therefore there was no interpersonal variability. In fact, the diagnosis was clinical in almost all cases, and PCR tests were only made in a few doubtful cases. Likewise, all clinical and cost data were collected by one person (clinical data by a dermatologist and costs by a pharmacist, P. Salvador) directly from the medical record. This avoided the biases that often occur in the transcription of data from the primary health-care or hospital registers to computerized databases.

The main weakness of the study is that data on the incidence of HZ were estimated by extrapolating from the data available in another Spanish region (Navarre).

However, the results of this study will be essential in order to make a cost-effectiveness study with the aim of establishing priorities in the administration of the HZ vaccine in people aged ≥ 50 y in Catalonia.

Methods

For the purposes of this study, HZ was defined as a vesicular rash with a metameric distribution usually presenting with pain at the site of the eruption. PHN was defined as a metameric pain that begins or persists at three months after the eruption of rash.

Estimation of the incidence of HZ

Currently available data do not allow an estimate of the real incidence of HZ in Catalonia.

In Catalonia, as in the rest of Spain, there is a public health system with universal coverage, but 25–27% of the population use private health care paid for by private health insurance. This sector of the population usually only require public medical care for severe problems (major burns, surgery, high-level surgery, complex treatments such as advanced cancer, organ transplantation, etc.). Thus, it may be supposed that around a quarter of

Table 5. Preventive potential of herpes zoster vaccine in preventing herpes zoster in persons aged ≥ 50 y according to the vaccination coverage reached

Age group (in years)	Estimated number of cases of HZ	Protective efficacy of the vaccine%	Cases prevented according to the vaccination coverage reached				
			20%	40%	60%	80%	100%
50–59	5984	70%*	838	1676	2513	3351	4189
60–69	6739	64%**	863	1725	2588	3450	4313
≥70	8809	38%**	669	1339	2008	2678	3347
≥50	21 532		2370	4740	7109	9479	11 849

Source: *Schmader et al.,[23] **Oxman et al.[20]

Table 6. Preventive potential of the herpes zoster vaccine in preventing postherpetic neuralgia in persons aged ≥ 50 y according to the vaccine coverage reached

Age group (in years)	Number of estimated cases of PHN	Protective efficacy of the vaccine%	Cases prevented according to the vaccination coverage reached				
			20%	40%	60%	80%	100%
50–59	735	66%*	97	194	291	388	485
60–69	805	66%**	106	213	319	425	531
≥70	1545	67%**	207	414	621	828	1035
≥50	3085		410	821	1231	1641	2052

*The study by Schmader et al. did not evaluate the protective efficacy of the HZ vaccine against PHN due to a lack of sufficient numbers. We applied the efficacy found in the study by Oxman et al. in the 60–69-y-age-group. Source: *Schmader et al.,[23] **Oxman et al.[20]

Table 7. Total cost of the diagnosis and treatment of the first 215 patients with HZ and PHN in the case series

Drug costs	28 704.53 euros
Antivirals	9628.05 euros
Oral analgesics	10 328.12 euos
Topical analgesics	8628.05 euros
Other drugs	1628.05 euros
Cost of clinical services	**49 656.23 euros**
Total costs	**78 360.73 euros**

Source: Case series of patients diagnosed in 10 basic health areas for which the Hospital del Sagrado Corazón de Barcelona serves as the reference center.

cases of HZ are attended by the private health sector, for which there are no morbidity data available. Therefore, the public data available clearly underestimate the incidence of HZ and its complications in Catalonia.

In Spain, incidence studies of HZ have been published based on data obtained from public primary healthcare centers in Valencia,[14-16] Madrid[17,18] and Navarre.[19] In Navarre, which has an excellent public health system, the proportion of patients seen by private family physicians and dermatologists is very low.

To estimate the real incidence of HZ in Catalonia, we extrapolated the incidence data from Navarre to the population of Catalonia.

Estimating the incidence of postherpetic neuralgia

The incidence of PHN was estimated by applying the proportion of cases of PHN diagnosed in a series of cases of HZ attended by the dermatology outpatient unit of the Hospital del Sagrado Corazón de Barcelona (Salleras M) to the total estimated number of cases of HZ. This unit attends cases from ten public basic health areas that serve a population of more than 150 000. The absolute numbers of cases of PHN were estimated by applying the absolute numbers of estimated cases of HZ extrapolated from the incidence in of Navarra to the population of Catalonia and the proportion of HZ cases that progressed to PHN in the case series mentioned. The incidence rates of PHN per 1000 inhabitants were calculated from the estimated absolute numbers and the population of Catalonia.

Estimation of costs

Costs were estimated by review of the medical records of the first 215 cases in the cases series. The review was made by a specialist pharmacist (P Salvador) who collected information on pharmaceutical treatments (antiviral drugs, topical treatments, analgesics and others) and medical visits to the dermatology outpatient unit of the Hospital del Sagrado Corazón de Barcelona

Table 8. Mean cost per patient of cases of HZ and PHN by age (in euros)

Age group (in years)	HZ		PHN	
	n	Cost per patient	n	Cost per patient
£35	15	219.49	-	-
36–49	20	223.97	-	-
50–64	48	250.78	3	820.82
≥65	110	344.01	19	931.79
All ages	193	301.52	22	916.66

Source: Case series of patients diagnosed in 10 basic health areas for which the Hospital del Sagrado Corazón de Barcelona serves as the reference center.

Table 9. Distribution of costs according to pharmacological and clinical components and clinical forms

	Patients without PHN		Patients with PHN	
	Cost	%	Cost	%
Drug costs	20 368.10	35%	9679.91	48%
Clinical costs	37 826.48	65%	10 486.56	52%
Total costs	58 194.58	100%	2016.47	100%

Source: Case series of patients diagnosed in 10 basic health areas for which the Hospital del Sagrado Corazón de Barcelona serves as the reference center.

Table 10. Estimated cost of HZ and PHN in persons ≥ 50 y in catalonia 2007–2013

Age group (in years)	HZ			PHN			Total cost HZ+PHN
	Cases	Mean cost	Total cost	Cases	Mean cost	Total cost	
50–64	9343	250.78	2 343 037.54	924	820.82	758 437.68	3 101 475.22
≥65	12 189	344.01	4 193 137.89	2161	931.79	2 013 598.19	6 206 736.08
≥50	21 532		6 536 175.43	3085		2 772 035.87	9 308 211.30

Source: **Tables 1 and 8**.

(and the services of ophthalmology, neurology, pain clinic, etc., to which patients were referred for treatment of complications).

The total cost of drug treatments and of visits to different hospital services for the diagnosis and treatment of each of the first 215 patients in the cases series, and the mean cost per patient according to the clinical form (HZ, PHN) were calculated.

The costs were estimated for the first 215 patients in the series (193 HZ and 22 PHN) treated during the period 2007–2011 according to the prices published by the Official Gazette of the General Council of the College of Pharmacists of Spain (retail price including VAT) during the study period.[32] The unit price was calculated based on the lowest reference price for the product. For topical products, the price of the largest pack was used, as it was proportionally more economical per unit.

The cost of clinical services was extracted from the tariffs of the Catalan Institute of Health.[33]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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